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PATENT COOPERATION TREATY

PCT

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
PP/2805 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01550	14/05/1999	15/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant NYCOMED AMERSHAM PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 9 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 1 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☒ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/09/1999	10.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Mundel, C Telephone No. +49 89 2399 7314

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01550

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-33	as originally filed				

Claims, No.:

2-19	as originally filed				
1	as received on	22/07/2000	with letter of	20/07/2000	

Drawings, sheets:

1/2,2/2	as originally filed

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

see separate sheet

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-19
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-14 and 17-19
	No:	Claims	15 and 16

2. Citations and explanations

see separate sheet

VI. Certain documents cited

1. Certain published documents (Rule 70.10)

and / or

2. Non-written disclosures (Rule 70.9)

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item II
Priority

The priority document of the present application was not available at the time where this International Preliminary Examination Report (IPER) has been drafted. The present analysis is based on the hypothesis that all the claims have a priority right corresponding to the date of filing of the priority document (15.05.98).

Re Item IV
Lack of unity of invention

According to **Rule 13 PCT** an application must relate only to one invention or to a group of inventions so linked as to form a **single inventive concept**, i.e. having at least one common technical feature defining a contribution over the known prior art.

In the present application, two groups of inventions have been identified.

A. Claims 1-16 refers to a compound of general formula Y-$(CR_2)_n$-X-NHJ - possibly in a radiometal complex - and to the use of said compound in the diagnosis of sites of thrombosis or embolism.

B. Claims 17-19 refers to a peptide fragment of α-antiplasmin, fibronectin, beta-casein, tetanus, amyloid, trappin or polyglutamine carrying a terminal metal complexing agent.

The single common concept linking the two groups of inventions can be seen as a peptide fragment of 3-45 amino acids comprising a metal-complexing agent. Such peptides comprising a metal-complexing agent were well-known in the art as exemplified in D1-D3. Thus, the common concept linking the two groups of invention can not be considered as inventive and the two groups mentioned above represent independent inventions.

Moreover, the attention of the applicant is drawn to the fact that the group B also lacks unity because the IPEA failed to see which is the common concept linking the different

peptides. Thus, each peptide carrying a terminal metal complexing agent represent an independent invention.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. **Reference is made to the following documents :**

   D1: J. LISTER-JAMES ET AL.: 'Pre-clinical evaluation of Technetium-99m platelet receptor-binding peptide' J. NUCLEAR MEDICINE, vol. 38, no. 1, January 1997 (1997-01), pages 105-111.

   D2: D.A. PEARSON ET AL.: 'Thrombus imaging using technetium-99m-labeled high-potency GPIIb/IIIa receptor antagonists.' J. MED. CHEM., vol. 39, 1996, pages 1372-1382.

   D3: WO 89 00051 A (CYTRX BIOPOOL LTD) 12 January 1989 (1989-01-12) cited in the application

   D1 discloses the structure of a compound : ^{99m}Tc-p748 and the pre-clinical studies of its use as hot spot scintigraphic thrombus imaging agent.

   D2 discloses the use of platelet-specific compounds which are radioabelled with γ-emitting radionuclides - and more particularly technetium-99m - for use for the non-invasive detection of thrombi.

   D3 discloses compounds for targeting deposits of fibrin. These compounds are substrate for the enzyme Factor XIIIa and contain at least the residues -Asn-Gln-Glu-Gln-.

2. The present application refers to compounds useful in the diagnosis of sites of venous and arterial thrombosis, embolism or infection, pharmaceutical composition containing them, their use in the diagnosis of diseases and methods for their preparation. Said compounds are synthetic analogues of lysine and glutamine with a suitable detectable moiety which function as substrates for the

enzyme Factor XIIIa.

3. The arguments of the applicant in response to the first communication received with the letter of the 20.06.00 have been taken into account for the drafting of the present International Preliminary Examination Report (IPER).

4. **Novelty; article 33(2) PCT.**

The subject-matter of claims 1-19 has never been disclosed in the documents cited in the International Search Report. Thus, claims 1-19 are considered as novel in the sense of article 33(2) PCT.

5. **Inventive step; article 33(3) PCT.**

The document D3 is considered as the most relevant document for the evaluation of the inventiveness of the claims. This document discloses compounds that are useful for targeting deposits of fibrin and which can be used to prepare diagnostic reagents that will bound to fibrin deposits (Abstract). These compounds are peptide which comprise at least the sequence -Asn-Gln-Glu-Gln- and one of these compounds is the N-terminal end of alpha-2 antiplasmin (p. 9, lines 1-9).
Moreover, D3 states that these compounds can be modified by inserting a group that can bind to radioactive atoms like technetium 99.
From the teaching of D3, the skilled person will have been prompted to identify groups that can bind to technetium. The document D2 discloses such groups (p. 1375, Figure 1 : Peptidyl chelating systems) and also states that technetium is a radionuclide of choice for imaging diagnostic (p. 1372, right-hand column, last paragraph).
Moreover, the adjunction of protecting groups to the termini of a peptide is **common practice** for the man skilled in the art and can not, therefore, be considered as inventive.
Thus, the skilled person will need no inventive step to combine the teaching of D3 and D2, arriving to the compounds claimed in the present application. Therefore, claims 1-19 can not be considered as inventive in the sense of article 33(3) PCT.

6. Industrial applicability; article 33(4) PCT.

Claims 15 and 16 refer to methods of diagnostic practised on the human or animal body.
For the assessment of the present claims 15 and 16 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VI
Certain documents cited

The attention of the applicant is drawn to the fact that the document cited below and mentioned in the search report can be used for the evaluation of the novelty of the claims during the regional phase at the EPO.

WO 98 31399 A (MENDIZABAL MARIVI ;WILSON IAN ANDREW (GB); GIBSON ALEX (GB); CHAMP). Publication date : 23.07.98. Priority date : 21.01.97. Filing date : 19.01.98.

Re Item VIII
Certain observations on the international application

Lack of clarity; article 6 PCT

1. Claim 1 refers to a compound of general formula Y-$(CR_2)_n$-X-NHJ. The scope of this claim is unclear for the following reasons :
   (i) It is not clear if the peptide, in the -$NH(B)_pZ^1$ or -$CO(B)_qZ^2$ groups, has to be linear or can be ramified since said peptidic part is not well defined.
   (ii) If the group X is C=O, the compound does **not necessarily** contain a metal complexing group what renders some compounds inadequate **for diagnostic imaging using radiometals.**

These remarks also applies to the independent claim 15 and to the dependent claims.

2. The compound of claim 1 can contain up to 45 amino acid residues. The IPEA is the opinion that, depending on the nature of said amino acid residues, some of the compounds of claim 1 will have a structure such that the glutamine/lysine-like residue will not be accessible for the factor XIIIa. Thus, all the compounds of claim 1 will not have the function disclosed in the present application. Moreover, the attention of the applicant is drawn to the fact that all the compounds disclosed in the examples of the present application contain less than 15 amino acid residues.

3. Claims 2-3 and 17-19 of the present application partially refer to very small peptides of 3 AAs carrying a terminal complexing agent. The IPEA considers that peptide fragments of 3 amino acid residues - which are not specific at all - carrying a "terminal metal complexing agent" have already been disclosed.

4. Claims 17-19 refer to peptide fragments containing 3-45 amino acid residues of α_2-antiplasmin, fibronectin, beta-casein, tetanus, amyloid, trappin or polyglutamin carrying a terminal metal complexing agent.
Said peptide fragments are not restricted to fragments containing a glutamine or lysine residue. Thus, some of these peptides will probably not be substrates of the enzyme Factor XIIIa and, therefore, not be useful in the diagnostic of sites of thrombosis or embolism.